Cigarette smoking, tar yields, and non-fatal myocardial infarction: 14 000 cases and 32 000 controls in the United Kingdom

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Abstract

***Objectives*—To assess the effects of cigarette smoking on the incidence of non-fatal myocardial infarction, and to compare tar in different types of manufactured cigarettes.**

***Methods*—In the early 1990s responses to a postal questionnaire were obtained from 13 926 survivors of myocardial infarction (cases) recently discharged from hospitals in the United Kingdom and 32 389 of their relatives (controls). Blood had been obtained from cases soon after admission for the index myocardial infarction and was also sought from the controls. 4923 cases and 6880 controls were current smokers of manufactured cigarettes with known tar yields. Almost all tar yields were 7-9 or 12-15 mg/cigarette (mean 7·5 mg for low tar (<10 mg) and 13·3 for medium tar (≥10 mg)). The cited risk ratios were standardised for age and sex and compared myocardial infarction rates in current cigarette smokers with those in non-smokers who had not smoked cigarettes regularly in the past 10 years.**

***Results*—At ages 30-49 the rates of myocardial infarction in smokers were about five times those in non-smokers (as defined); at ages 50-59 they were three times those in non-smokers, and even at ages 60-79 they were twice as great as in non-smokers (risk ratio 6·3, 4·7, 3·1, 2·5, and 1·9 at 30-39, 40-49, 50-59, 60-69, 70-79 respectively; each $2P < 0{\cdot}00001$). After standardisation for age, sex, and amount smoked, the rate of non-fatal myocardial infarction was 10·4% (SD 5·4) higher in medium tar than in low tar cigarette smokers ($2P = 0{\cdot}06$). This percentage was not significantly greater at ages 30-59 (16·6% (7·1)) than at 60-79 (1·0% (8·5)). In both age ranges the difference in risk between cigarette smokers and non-smokers was much larger than the difference between one type of cigarette and another (risk ratio 3·39 and 3·95 at ages 30-59 for smokers of similar numbers of low and of medium tar cigarettes, and risk ratio 2·35 and 2·37 at ages 60-79). Most possible confounding factors that could be tested for were similar in low and medium tar users, with no significant differences in blood lipid or albumin concentrations.**

***Conclusion*—The present study indicates that the imminent change of tar yields in the European Union to comply with an upper limit of 12 mg/cigarette will not increase (and may somewhat decrease) the incidence of myocardial infarction, unless they indirectly help perpetuate tobacco use. Even low tar cigarettes still greatly increase rates of myocardial infarction, however, especially among people in their 30s, 40s, and 50s, and far more risk is avoided by not smoking than by changing from one type of cigarette to another.**

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Introduction

In countries such as the United Kingdom, where cigarettes have been used widely for several decades, tobacco now accounts for about 30% of all deaths in middle age, with lung cancer and coronary heart disease the most common fatal conditions.[1-3] Over the past few decades cigarettes have been altered in various ways, reducing the so called yields of tar and nicotine when smoked in a standard way by a machine. Typical British cigarettes had tar yields of 25-35 mg during the 1950s and 5-15 mg in 1990.[4] But, partly because the chief toxins in cigarette smoke are uncertain and partly because smokers may compensate for reduced yields (or other changes) by smoking cigarettes more actively,[5-10] the health effects of alterations in cigarette manufacture are unpredictable. Low tar cigarettes do cause substantial risks of cancer and heart disease, although the risk of lung cancer is less than with high tar cigarettes.[3 11-14] For heart disease, however, there remains uncertainty[15-17] about whether the rates have been decreased, increased, or not changed by alterations in cigarette composition over the past few decades. National heart disease mortality rates and trends are not informative because other factors cause such large differences in coronary heart disease between different populations and time periods. Instead, concurrent epidemiological comparisons within one population are needed.

But, although tobacco is a major cause of heart disease, particularly among young and middle aged adults, it is difficult for conventional prospective or retrospective studies to compare the risks from different types of cigarette. Only a narrow range of cigarette tar yields is concurrently available within one population, and the tar yields of cigarettes smoked by people in 1990 might correlate poorly with the tar yields smoked by these people years earlier. Hence, even large differences in risk between prolonged use of low, medium, and high tar cigarettes might produce only small differences in risk between current use of low and medium tar cigarettes. At younger ages the proportional difference in rates of coronary heart disease between smokers and non-smokers is particularly extreme, so any effect of cigarette type may also be extreme. Thus, to minimise the chances of a false negative result in a study of tar yields, the number of cases of myocardial infarction in middle aged cigarette smokers should be large—preferably several thousand—with at least as many controls. We achieved this by studying subjects from the United Kingdom who participated in the large ISIS (international studies of infarct survival) trials of the treatment of acute myocardial infarction,[18-20] by using postal questionnaires (copies available on request), rather than interviews, and by simplifying blood collection procedures.

Patients and methods

CASES AND CONTROLS

Cases were the survivors in the United Kingdom aged 30-79 from the ISIS-3 or ISIS-4 trials who completed an epidemiological questionnaire sent to them a few months after their infarction. Those who were asked to complete it were all the survivors from ISIS-3, but from ISIS-4 only the survivors aged 30-59 who on admission to hospital were reported to be cigarette smokers. Thus, although only cases from ISIS-3 can be used to compare smokers with non-smokers, the cases from ISIS-4 strengthen the analyses of tar yields among smokers aged 30-59. The ISIS-3 questionnaire asked the cases to identify all their brothers, sisters, and children aged at least 30 who were resident in the United Kingdom. A similar "control" questionnaire was then sent to such relatives, accompanied by a second copy, which the relatives, if married, were to ask their spouse to complete. One reminder was sent to cases and relatives who did not reply, and inconsistencies or omissions were queried once.

Of the 20 681 ISIS-3 patients in the United Kingdom, 19 065 who were not known to be dead were posted the case questionnaire, of whom 1346 were found to be dead and 13 969 (79% of presumed survivors) completed it. The control questionnaire was sent to 30 247 relatives of ISIS-3 cases, of whom 75 were found to be dead and 21 995 (73% of presumed survivors) and 14 245 of their spouses completed it. Patients with a history of stroke, gastrointestinal bleeding, or ulcer tended not to have been recruited into the ISIS-3 trial,[19] and so people with such conditions were not eligible as cases or controls. Of those who completed questionnaires, 2002 cases and 3851 controls were excluded because they were under 30, over 79, or of unknown age or because they had a self reported history of "definite stroke" or of "bleeding or ulcer in (or near) the stomach."

ISIS-4 patients in the United Kingdom aged 30-59 who were described at trial entry as current smokers were also sent the questionnaire. The response rate for such patients was similar in both trials. Any of these ISIS-4 patients whose questionnaire response indicated that they were not cigarette smokers at the time of their infarction were excluded. ISIS-4 (and, to some extent, ISIS-3) tended to exclude patients with shock or persistent hypotension,[20] but such exclusions should not bias the epidemiological analyses of tobacco use.

BLOOD SAMPLES

Blood was to be taken from patients in ISIS-3 immediately after randomisation but before the trial treatments and collected in a 10 ml vacutainer containing 0·12 ml preservative (15% potassium EDTA with aprotinin 0·34 mmol/l: Becton Dickinson). On returning their questionnaire, controls were sent an identical container for their general practitioner to collect blood. Case and control containers were sent by first class post to Oxford. Controls were sent one reminder about giving a sample. After a mean of two days in the post the blood was centrifuged, the packed cell volume was recorded, and the plasma and buffy coat were aliquoted for storage at −40°C. Blood arrived from 97% of ISIS-3 cases and 45% of controls, but breakages or haemolysis rendered 6% of these samples unusable. The present blood analyses involve only correlations of smoking with blood biochemistry results, and these analyses should not be materially biased by low response rates.

Plasma cotinine concentration was measured in controls who were current cigarette smokers, and in a 3% sample of controls who reported no current use of tobacco, by means of antibodies developed by Knight *et al* in a modification for plasma of their urinary radioimmunoassay.[21] Results with this plasma assay correlate closely with those with gas chromatography.[22] Beckman CX-4 and CX-5 autoanalysers were used for measuring concentrations of cholesterol and albumin (both with Beckman reagents) and apolipoproteins A_1 and B (with Immuno reagents). To correct for discoloration from haemolysis, an initial blank reading was subtracted from the final reading. Samples from a large plasma pool were included in each analytical run, yielding coefficients of variation of 2% for cholesterol and albumin and 4% for apolipoproteins.

QUESTIONNAIRES

Information was sought on sex, age, body size, smoking, drinking, past health, and relatives. Cases were asked about their habits and history just before their index myocardial infarction (because having a heart attack may alter a patient's habits), while controls were asked about their present habits. Hence, questions to cases often began, "Before your recent hospital admission. . . ." Both cases and controls were asked to list how many relatives of certain types they had, but only cases were to provide contact details. In other respects case and control questionnaires were identical. The medical history section was non-technical and recorded various conditions that might be associated with exclusion from the randomised trial (see above) or that might affect, or be affected by, smoking. After the question of whether they had "ever smoked regularly (ie on most days for at least a year)" the rest of the cigarette section was to be completed only by those who replied "yes." It dealt with the age at which the subject had first and last smoked regularly, whether any cigarettes had been smoked in the previous month, the number smoked per day when the subject had last smoked cigarettes regularly, and the way in which cigarettes were smoked. People were to tick against 137 detailed brand names the one that, when they last smoked, they usually smoked most of—or, if it was not on the list, to write out its exact name (and, whenever possible, to enclose the packaging of that brand with the questionnaire). For the few who listed more than one brand, the average of the yields was taken. Ninety eight per cent of controls and 98% of cases who currently smoked only manufactured cigarettes with a known tar yield, and both reported using their current brand for, on average, the past 10 or 11 years.

DEFINITIONS OF CIGARETTE SMOKING STATUS

Respondents were classified as current cigarette smokers (26% of the controls: those who had smoked cigarettes in the previous month, plus the few who failed to answer this yes/no question but gave other evidence of current cigarette use); other tobacco users (3%: pipes, cigars, or smokeless tobacco in the past year); or as not using tobacco (71%: all others). In table I these are further subdivided. Because of the possible confusion between those who stopped smoking many years ago and those who never smoked, the main comparison group was defined as non-smokers who had not used cigarettes regularly in the past 10 years.

ESTIMATED 1990 TAR YIELDS

The United Kingdom's government chemist conducts surveys of common cigarette brands, measuring tar, nicotine, and carbon monoxide yields, twice a year (R Waller, personal communication). During the late 1980s the annual decrease in sales weighted yields was about 2-3% for tar, 1-2% for nicotine, and zero for carbon monoxide (J Rentoul, personal communication).[4] Most ISIS-3 cases replied in 1990 about habits

before their myocardial infarction (mean date of infarction: February 1990), most controls replied in 1990-1 (mean: November 1990), and most ISIS-4 cases replied in 1992-3 (mean date of infarction: July 1992). To avoid secular trends in yields introducing minor biases, the mid-1990 survey results for each cigarette brand were used (R Waller, personal communication). If a brand was assayed only earlier or later than mid-1990, yields from the closest survey were extrapolated to mid-1990 by annual decreases of 2·5% in tar and 1·5% in nicotine.

RESURVEY OF CONTROLS A FEW YEARS LATER

To check reproducibility, about 2000 controls who originally returned both questionnaire and blood sample (and whose replies indicated no previous vascular disease) were sent the same questionnaire and blood kit again about 2-3 years later. To avoid oversampling young controls, the random sample was stratified with respect to sex and age in groups of five years. Seventy per cent (1388/1996) returned the questionnaire, 95% (1324/1388) of whom gave blood.

STATISTICAL METHODS

The analyses are all unmatched—that is, they compare cases with all controls, not just with their own relatives—and for tar yield analyses among smokers the controls are as relevant to ISIS-4 as to ISIS-3 cases. All analyses of myocardial infarction rates were stratified either for sex and five year age group or for these factors and amount smoked (five categories; see below). Calculations of risk ratios—or, equivalently, relative risks—entailed unmatched stratified logistic regression (fitted by unconditional maximum likelihood), with one extra term included for each stratum. Risk ratios are often given with 95% confidence intervals. Two sided probability values (2P) are used.

Results

FREQUENCY DISTRIBUTIONS OF SMOKING HABITS

Table I shows the numbers of controls and cases in various categories of tobacco use subdivided by sex and by age. The age range of chief relevance to the tar yield analyses is 30-59, and among controls in this range 28% both of men and of women were current cigarette smokers, in close agreement with nationally representative, interviewer administered surveys in the early 1990s.[23] Twenty two per cent of these controls were current users of manufactured cigarettes only with known tar yields.

Figure 1 gives, for controls who currently used manufactured cigarettes only, the frequency distribution of (*a*) the reported number smoked per day and (*b*) the estimated 1990 tar yield. Self reported cigarette consumption was categorised as 1-9, exactly 10, 11-19, exactly 20, and ≥21 cigarettes a day; 85% reported smoking 10-30 cigarettes a day. The tar yields show a bimodal distribution, with commonest values 7-9 or 12-15 mg/cigarette. Tar yields of 10 mg were rare, which makes this a natural point of subdivision, unaffected by any slight differences in dates of case and control responses, to define two main categories: low tar (< 10 mg, mean 7·5 mg) and medium tar (≥ 10 mg, mean 13·3 mg). Medium tar is sometimes split into 10-12, 13, and ≥ 14 mg/cigarette. This definition of low tar is also used by the Department of Health (R Waller, personal communication).[4] Twenty five per cent of the smokers in figure 1b use low tar cigarettes, as in the nationally representative survey in 1990.[23] Almost all

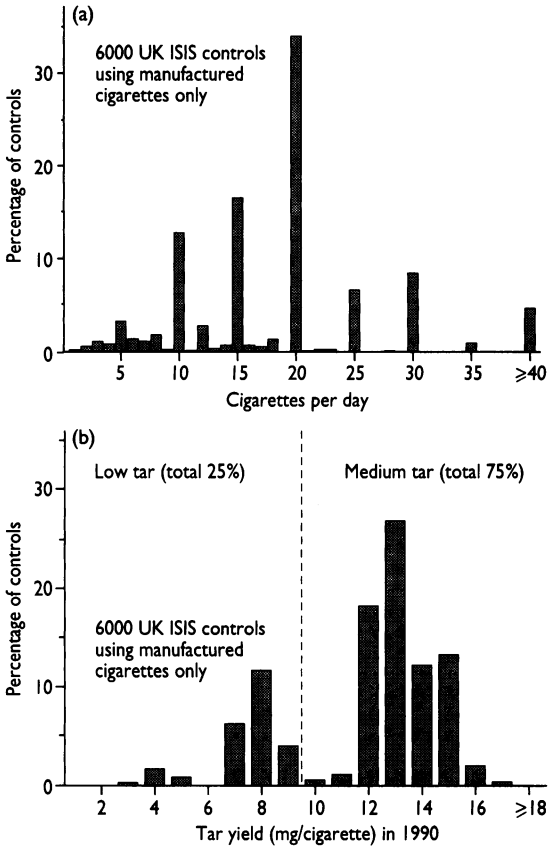

FIG 1—*Replies by controls who smoked manufactured cigarettes only. (a) Reported daily cigarette use (34% reported 20 cigarettes per day, and 85% reported 10-30). (b) Tar yields in 1990 of the brands reported*

TABLE I—*Tobacco use in cases and controls aged 30-79 with questionnaires returned*

	Current cigarette smoker				Other tobacco		Not using tobacco			
	Manufactured cigarettes and no other tobacco		Other cigarette users	% Now using any cigarettes	Smoking pipe or cigar but no cigarettes	Using smokeless tobacco only	Former regular cigarette smoker		Never regular cigarette smoker	Total*
	Tar known	Tar unknown					< 10 years ago	≥ 10 years ago		
Controls:	6880	162	1389	26	1031	71	3181	5502	14173	32389
Men 30-59	2184	35	958	28	676	40	1128	1785	4357	11163
Women 30-59	3264	60	153	28	11	1	1145	1385	6559	12578
Men 60-79	563	21	251	20	337	28	465	1506	906	4077
Women 60-79	869	46	27	21	7	2	443	826	2351	4571
ISIS-3 cases:	3453	65	1063	38	859	48	1311	2070	3098	11967
Men 30-59	1351	23	619	48	405	26	424	467	804	4119
Women 30-59	520	8	33	60	0	0	98	47	236	942
Men 60-79	858	16	382	27	450	20	537	1268	1171	4702
Women 60-79	724	18	29	35	4	2	252	288	887	2204
ISIS-4 cases:	1470	34	455	—	—	—	—	—	—	1959
Men 30-59	1117	29	430	—	—	—	—	—	—	1576
Women 30-59	353	5	25	—	—	—	—	—	—	383
Total	11803	261	2907	—	1890	119	4492	7572	17271	46315

*Current users and non-users.

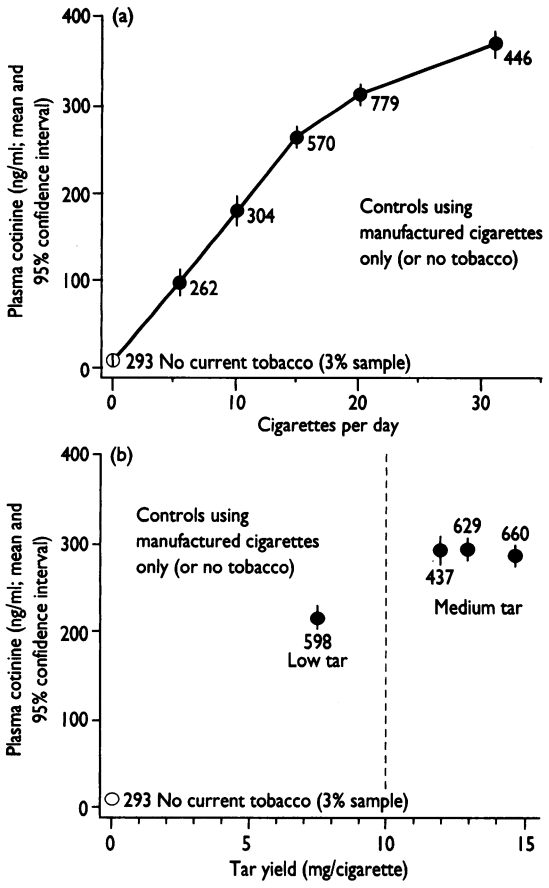

FIG 2—*Cotinine by cigarette smoking habit in controls. (a) Cotinine versus daily cigarette use. (b) Cotinine versus tar yield of reported brand. In the low and medium tar smokers whose blood samples were assayed, mean plasma cotinine concentrations were 217 and 292 ng/ml, mean cigarettes a day were 15·8 and 18·7, and mean yields per cigarette were 7·4 and 13·3 mg tar, 0·75 and 1·18 mg nicotine, and 8·4 and 15·0 mg carbon monoxide. Blood was taken on average of eight months after questionnaire, and in 12 out of 293 whose questionnaire had indicated no smoking cotinine concentration (mean 208 ng/ml) indicated current tobacco use*

TABLE II—*Non-fatal myocardial infarction: age-specific effect of cigarette use in people with no history of major neoplastic or vascular disease*

	Current smoker of manufactured cigarettes only		Non-smoker with no regular cigarette use in past 10 years		Myocardial infarction*	
Age (years)	Cases	Controls	Cases	Controls	Risk ratio (95% confidence interval)	Test statistic†
30-39	78	1784	35	4873	6·33 (4·22 to 9·51)	8·9
40-49	293	1497	190	4306	4·66 (3·82 to 5·69)	15·1
50-59	435	861	508	2701	3·10 (2·64 to 3·65)	13·7
30-59	806	4142	733	11880	3·85 (3·41 to 4·34)	22·1
60-69	416	653	707	2299	2·54 (2·16 to 2·98)	11·3
70-79	111	163	369	942	1·92 (1·45 to 2·54)	4·6
60-79	527	816	1076	3241	2·37 (2·06 to 2·72)	12·1

*Smoker *v* non-smoker rates standardised for age and sex.
†Number of standard deviations by which the logarithm of the risk ratio differs from zero.

used filtered brands (100% of the low tar group, 96% of the medium tar group), so filters accounted for little of the difference in yields between low and medium tar cigarettes in 1990.

RELATION BETWEEN QUESTIONNAIRE AND COTININE CONCENTRATIONS

Figure 2 shows the relation between plasma cotinine concentrations and (*a*) reported daily cigarette use and (*b*) tar yield for controls reporting use of manufactured cigarettes only or no current tobacco use. The mean cotinine concentration was very low in the self reported non-smokers, which helps validate both questionnaire and laboratory results. Among cigarette smokers there was a strong relation between cotinine concentration and the amount reported to be smoked, which again helps validate the questionnaire. The downward curvature in figure 2a suggests that those who smoke more cigarettes may absorb less nicotine from each one or that those reporting large numbers include disproportionately many who overreported, or both. Either way, self reported cigarette consumption provides only approximate information about the real doses of nicotine and of other substances.

In figure 2b the mean cotinine values were about a third higher among the controls who smoked medium tar cigarettes (low tar 217 ng/ml *v* medium tar 292 ng/ml). But the smokers of low tar cigarettes reported smoking 15·8 cigarettes a day compared with 18·7 a day for those in the medium tar group. After standardisation for age, sex, and amount smoked, however, the mean plasma cotinine concentration was still 19% higher with medium tar cigarettes. This difference in cotinine is still highly significant ($2P < 0{\cdot}00001$), which helps validate the categorisation of tar yield based on the questionnaire. But it is less extreme than the difference of over 50% in the nicotine yield per cigarette measured by machine (0·75 mg and 1·18 mg). This may be partly because the categorisation of tar yields is imperfect, and partly because smokers of low yield cigarettes compensate by taking in more smoke per cigarette. But, since this categorisation predicts highly significant biochemical differences in blood taken months later (figure 2b), it has some validity.

CIGARETTE USE AND NON-FATAL MYOCARDIAL INFARCTION

When those using manufactured cigarettes only were compared with non-smokers who had not smoked cigarettes regularly in the past 10 years (excluding in both cases those using any other type of tobacco), the relative risks for non-fatal myocardial infarction in people with no previous neoplastic or major vascular disease depended strongly on age (table II, fig 3). As is the case for mortality from coronary heart disease,[1,2] the risk ratio comparing smokers with non-smokers was greater at younger ages, reinforcing the need for the relevance of tar yields to be considered separately at younger and older ages.

TAR YIELDS AND NON-FATAL MYOCARDIAL INFARCTION

Information about the relevance of tar yields comes from current users of manufactured cigarettes only. Of these, much the most informative are the 9000 aged 30-59, rather than the 3000 aged 60-79. This is not only because the numbers are larger but also because the risk ratio when smokers are compared with non-

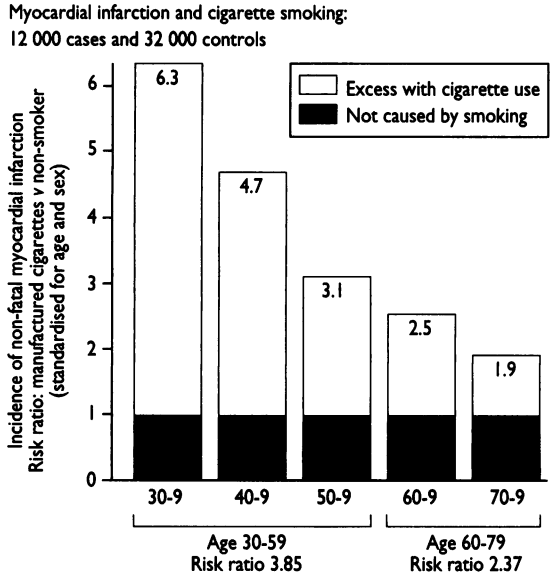

FIG 3—*Cigarettes and non-fatal myocardial infarction as a first event: risk ratios at various ages. Results in people with no previous history of major neoplastic or vascular disease. Each risk ratio is standardised for sex and for quinquennium of age, and compares those using manufactured cigarettes only with those who were not currently using any tobacco and had not been regular cigarette smokers at any time in the past 10 years. Risk ratio is given within each column. (As all cases recruited from ISIS-4 were cigarette smokers, this figure involves cases only from ISIS-3)*

TABLE III—*Comparison of myocardial infarction rates in current smokers of medium and low tar cigarettes*

	No currently using manufactured cigarettes only, with known 1990 tar yield			Ratio of non-fatal myocardial infarction in smokers of medium tar v smokers of low tar cigarettes (with 95% confidence interval and significance)		
	"Cases" of infarction* ISIS-4	"Cases" of infarction* ISIS-3	Controls (no infarction)	Standardised for age and sex only	Standardised for age, sex, and amount smoked	Standardised for age, sex, and amount smoked: no previous disease†
Age 30-59:				1·203	1·166	1·075
Low tar	274	359	1268	(1·061 to 1·364)	(1·025 to 1·326)	(0·900 to 1·283)
Medium tar	1196	1512	4180	2P=0·004	2P=0·02	2P>0·1
Age 60-79:				1·046	1·010	1·010
Low tar	—	438	433	(0·890 to 1·230)	(0·856 to 1·191)	(0·771 to 1·323)
Medium tar	—	1144	999	2P>0·1	2P>0·1	2P>0·1
Age 30-79:				1·142	1·104	1·055
Low tar	274	797	1701	(1·034 to 1·260)	(0·998 to 1·222)	(0·910 to 1·223)
Medium tar	1196	2656	5179	2P=0·008	2P=0·06	2P>0·1

*Proportions smoking low tar rather than medium tar cigarettes were similar in ISIS-4 and ISIS-3: after standardisation for age, sex, and amount smoked, the odds ratio comparing the two tar yield categories in the two studies was 1·000 (SD 0·091).
†For comparison of the effects of different tar yields, inclusion of patients with some previous neoplastic or vascular disease may well produce no material bias and helps stabilise the estimates.

TABLE IV—*Associations between smoking habits and blood lipid concentrations. Values are means (SE) standardised for age, sex, and case-control status*

	Cigarette use			Cigarette tar yield		
Lipid measurement	Current smoker of manufactured cigarettes only (n=1256)	Non-smoker with no cigarette use in past 10 years (n=3183)	Significance	Low tar (n=295)	Medium tar (n=942)	Significance
Cholesterol (mmol/l)	5·92 (0·03)	5·91 (0·02)	NS	6·01 (0·06)	6·02 (0·03)	NS
Apolipoprotein A_1 (g/l)	1·273 (0·006)	1·288 (0·004)	2P=0·05	1·266 (0·013)	1·264 (0·007)	NS
Apolipoprotein B (g/l)	1·194 (0·008)	1·165 (0·005)	2P=0·004	1·222 (0·016)	1·226 (0·009)	NS

TABLE V—*Reproducibility of smoking classification*

	Response to original questionnaire				
	Currently using tobacco		Not using tobacco		
Response to repeat questionnaire 2-3 years later	Manufactured cigarettes only	Other tobacco user	Former cigarette smoker		Never cigarette smoker
			<10 years	≥10 years	
Manufactured cigarettes only	99*	9	8	5	0
Other tobacco user	1	86	7	3	3
Former cigarette smoker:					
<10 years	22	12	50	11	0
≥10 years	2	18	37	370	15
Never cigarette smoker	4	9	2	24	591

*Ninety seven of these had known tar yield at both enquiries (65 classified as medium tar originally and medium tar later, 21 as low then low, 8 as medium then low, 3 as low then medium).

smokers is more extreme in middle than in old age. As there was no significant difference between the tar yields of cases aged 30-59 in ISIS-3 and in ISIS-4 (table III), the groups were combined.

Table III provides age-sex standardised comparisons of non-fatal myocardial infarction in smokers of low tar versus smokers of medium tar cigarettes. Overall, there were only slight effects of the tar yield. The mean daily number of cigarettes smoked was slightly higher in the medium tar than in the low tar cigarette smokers (19·0 *v* 17·1). When standardised not just for age and sex but also for the daily number of cigarettes smoked, the incidence of myocardial infarction was 10·4% (SD 5·4) higher in medium than in low tar cigarette smokers (2P=0·06). This difference was non-significantly greater at ages 30-59 (16·6% (7·1) higher; 2P=0·02) than at 60-79 (1·0% (8·5) higher; 2P>0·1) (fig 4). As these two results are not significantly different from each other, they do not prove that tar yields are of greater proportional importance to the cardiotoxicity of cigarettes in middle than in old age, especially since the smoker versus non-smoker risk ratios are less extreme in old age. In both age ranges the difference between cigarette smokers and non-smokers was much larger than the difference between one type of cigarette and another: the risk ratios were 3·39 and 3·95 for smokers of similar numbers of low and of medium tar cigarettes at ages 30-59 and were 2·35 and 2·37 at ages 60-79. (Table III shows that results were similar when these comparisons were based on the smaller numbers of cigarette smokers with no reported history of neoplastic or major vascular disease.)

POTENTIAL CONFOUNDING FACTORS

Table IV relates smoking to blood lipid concentrations among ISIS-3 cases entering the trial within 0-4 hours of pain onset whose blood spent only one or two days in the post, and among one randomly chosen control per case (matched for age, sex, and days sample spent in the post). Apolipoprotein A_1 was 1·2% lower and apolipoprotein B 2·4% higher in smokers than in non-smokers, but these differences are too small to account for much of the excess risk among smokers.

There were no significant differences in blood lipid concentrations (or albumin concentration, data not shown) between smokers of low and of medium tar cigarettes, either overall or in those aged 30-59 (data not shown). For many factors there were likewise no significant differences between smokers of low and medium tar cigarettes. These include self reported height, weight, loneliness, depression, worry, insomnia, teenage acne, tea consumption, alcohol consumption, and whether living with a spouse. For a few factors, however, there were definite differences even after standardisation for age and sex. (Multivariate adjustment for these observed differences would make little difference, but these differences point to the possibility of others existing.) Those who smoked low tar cigarettes were, on average, almost six months older when they left full time education (mean leaving age 15·9 years for low tar group *v* 15·5 years for medium tar), were more likely to say that they had matured physically "later than average" (13·4% *v* 10·5%), had "softer hands than average" (14·4% *v* 11·0%), had been regular drinkers of coffee (75% *v* 67%), were older when they started to smoke (18·8 *v* 17·9 years old), and had changed to their current brand more recently (7·9 *v* 10·1 years previously). These suggest a general tendency for those who smoke medium tar cigarettes to include a slightly larger proportion of manual workers, and to have slightly less education. (Likewise, unpublished analyses by M Jarvis of the 1990 and 1992 general household surveys in the United Kingdom found significantly higher "indices of deprivation" in users of medium than of low tar cigarettes.)

REPRODUCIBILITY OF SMOKING CLASSIFICATION

A total of 1388 controls repeated the questionnaire a few years later, and table V compares their two replies. When subdivided three ways (manufactured cigarettes only; other tobacco or ex-cigarette smoker <10 years; remainder), 90% remained in the same category; of the 97 who smoked only manufactured cigarettes with tar known on both occasions, 89% had continued to smoke medium or low tar cigarettes as originally. Overall, there was a 5% shift towards the low tar category, in line with national trends, and the correlation coefficient between the two assessments of tar yield was 0·71.

Discussion

When cigarette smokers are compared with non-smokers the risk ratio for myocardial infarction is much more extreme in early adult life than in old age. The numbers contributing to figure 3 are unusually large (12 000 cases and 32 000 controls) and so the pattern of steadily increasing risk ratio with younger

age is particularly reliably demonstrated, as are the hazards at the extremes of the age range of 30-79. The risk ratio is twofold at ages 70-79, but it is almost fourfold at ages 30-59 (threefold at 50-59 but fivefold at 30-49). Even these large differences have probably been somewhat diluted by the misclassification of some smokers or non-smokers. Had it been possible, with no classification errors, to compare persistent cigarette smokers with lifelong non-smokers then the risk ratios would probably have been still more extreme than those in figure 3, and would have been at least fourfold at ages 30-59. As most of the excess risk associated with smoking is caused by smoking,[1,2] this fourfold risk ratio implies that about three quarters of the myocardial infarctions among cigarette smokers aged 30-59 were caused by tobacco (two thirds at ages 50-59, but four fifths at ages 30-49).

Any differences in the risk of heart disease between those who are smoking different types of cigarette must be much less extreme than the differences between smokers and non-smokers, so especially large studies are needed to assess them. Moreover, epidemiological studies that were undertaken when tar yields below 15 mg were still uncommon (N J Wald *et al*, unpublished data)[24-30] are of limited contemporary relevance in countries such as the United Kingdom where tar yields above 15 mg have already virtually disappeared (fig 1b) and where a European Union upper limit of 12 mg is soon to be enforced. As no other large recent studies are available, our current findings stand alone.

For tar yields the central finding is that after standardisation for age, sex, and number of cigarettes, the incidence of non-fatal myocardial infarction seemed to be about 10% greater with medium tar than with low tar cigarettes (95% confidence interval 0 to 22%, table III). Even if this 10% difference was highly statistically significant (which it is not: 2P=0·06) it would still not be epidemiologically secure. It is uncertain how much selective emphasis to put on the data at ages 30-59 as opposed to those at 60-79, how much selective emphasis to put on the data from people with no previous disease, and how much to emphasise

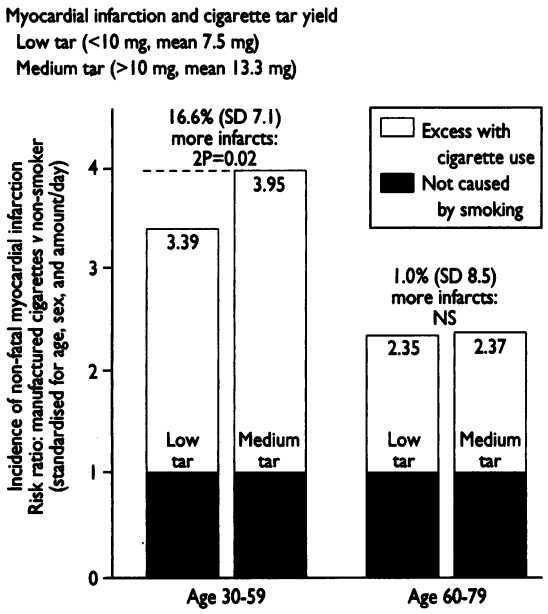

FIG 4—*Cigarette tar yields and risk of non-fatal myocardial infarction. Standardised for age, sex, and amount smoked, comparisons at ages 30-59 indicate that non-fatal myocardial infarction rates were 1·166 (SD 0·071) times as great among medium tar as among low tar cigarette smokers (2P=0·02; table III). The same standardised comparisons at ages 60-79 give 1·010 (0·085) (NS). These two estimates (1·166 and 1·010) are combined with the risk ratios of 3·85 and 2·37 for cigarette smokers versus non-smokers (fig 3) to yield the cited risk ratios for smokers of low and medium tar cigarettes: 3·39 and 3·95 at ages 30-59 and 2·35 and 2·37 at ages 60-79*

Key messages

- Non-fatal myocardial infarction rates are five times as great among cigarette smokers as among non-smokers at ages 30-49, three times as great at ages 50-59, and twice as great at ages 60-79
- Among cigarette smokers four fifths of myocardial infarctions at ages 30-49 were caused by tobacco, two thirds at ages 50-59, and half at ages 60-79
- The risks seem to be slightly greater with medium tar than with low tar cigarettes, but this difference is not definite
- Differences in risk between cigarette smokers and non-smokers are far greater than any differences in risk between one type of cigarette and another
- Far more myocardial infarctions could be avoided by not smoking than by changing from one type of cigarette to another

analyses that are standardised for the amount smoked. (Those using low tar cigarettes reported smoking slightly fewer than those smoking medium tar cigarettes, and if lower daily consumption is chiefly a consequence of lower yields of tar, nicotine, and other smoke components then it should not be standardised for.) Hence, table III reports several different comparisons of disease rates in smokers and in non-smokers, with differences that are sometimes more and sometimes less than 10%. Also, there was a slight tendency for tar yields to be inversely related to education and to various other aspects of social class. It is difficult to see how some of these uncertainties can be resolved: large scale randomisation is impracticable, and even if the present study could have been much larger, thereby narrowing the confidence intervals, the possibility of confounding would remain.

Despite these uncertainties, however, the present results provide some reassurance to those in government or in industry who could direct decreases in cigarette tar yields to reduce cancer incidence.[3,11-14] They indicate that such changes will not substantially increase the incidence of myocardial infarction and may well decrease it. Thus, the limit of 12 mg/cigarette on tar yields that is now being introduced in the European Union should help limit the number of premature deaths from tobacco, unless governments or smokers come to regard reductions in tar yield as substitutes for the avoidance of cigarettes, for in developed countries tobacco remains much the most important cause of premature death. This is particularly so for men, with tobacco now causing about a third of all deaths in middle aged men. But where women have been smoking cigarettes for some decades (as, for example, in the United Kingdom or the United States) tobacco also already causes about a quarter of all the deaths in middle aged women.[1]

For the general population, therefore, the most important finding is not the slight and uncertain difference in figure 4 between one type of cigarette and another but the large and definite difference in figure 3 between cigarette smokers and non-smokers, particuularly in early middle age. Irrespective of whether low or medium tar cigarettes are used, about three quarters of the smokers who have a heart attack in their 30s, 40s, or 50s need not have done so, and far more heart attacks could be prevented by not smoking than by reducing cigarette tar yields.

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relatives who collaborated in this study, and to the medical and nursing staff from more than 100 hospitals in the United Kingdom listed in the ISIS reports.[19,20] We particularly thank Peter Froggatt, Cheryl Swann, and Robert Waller of the Independent Scientific Committee on Smoking and Health, Department of Health; Keith Darrall of the Laboratory of the Government Chemist; Martin Jarvis of the Imperial Cancer Research Fund; and Kuldip Bhamra, Vanessa Boag, Lee Buckingham, Mary Burton, Sarah Clark, Sarah Edwards, Sheila Foster, Heather Halls, Mavis King, Karen Kourellias, Christine Marsden, Gale Mead, Kevin Murphy, Martin Radley, and Karl Wallendszus of the Oxford Clinical Trial Service Unit and Epidemiological Studies Unit.

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A 28 year follow up of mortality among women who smoked during pregnancy

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Abstract

***Objective*—To investigate long term mortality among women who smoked during pregnancy and those who stopped smoking.**

***Design*—A follow up of a geographically defined cohort from 1966 through to 1993.**

***Subjects*—11 994 women in northern Finland expected to deliver in 1966, comprising 96% of all women giving birth in the area during that year. Smoking habits were recorded during pregnancy but not later.**

***Main outcome measure*—Mortality by cause (571 deaths).**

***Results*—The mortality ratio adjusted for age, place of residence, years of education and marital status was 2·3 (95% confidence interval 1·8 to 2·8) for the women who smoked during pregnancy and 1·6 (1·1 to 2·2) for those who stopped smoking before the second month of pregnancy, both compared with non-smokers. Among the smokers the relative mortality was higher for typical diseases related to tobacco intake, such as respiratory and oesophageal cancer and diseases of the cardiovascular and digestic organs and also for accidents and suicides.**

***Conclusion*—The risk of premature death seems to be higher in women who smoke during pregnancy than in other women who smoke. This may be explained either by the low proportion of those who stop later and the high proportion of heavy smokers or by other characteristics of these subjects that increase the risk.**

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Introduction

The consequences for the child of maternal smoking during pregnancy have been well documented,[1] but less interest has been directed towards the mothers' prognosis. We analyse here 28 year mortality data on a geographically defined population of women who smoke during pregnancy; many background variables were recorded prospectively.

Methods

Population—The cohort consisted of 12 055 pregnant women (13 of them delivering twice) in the two most northern provinces in Finland, Oulu and Lapland, whose expected dates of delivery fell in 1966 and when the pregnancy resulted in a birth. The cohort covered 96% of all deliveries in the region in 1966.[2] The